



Atty. Dkt. No. 075405-1103

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant: Francis S. Markland, et al.  
Title: Contortrostatin and Methods for its  
Use in Preventing Metastasis and  
Other Conditions  
Appl. No.: 10/712,584  
Filing Date: 11/12/2003  
Examiner: Michael L. Borin  
Art Unit: 1631

<p><b>CERTIFICATE OF MAILING</b> I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date below.</p> <p><u>Vanessa Agha</u> (Printed Name)</p> <p><u>Vanessa E. Agha</u> (Signature)</p> <p><u>March 14, 2006</u> (Date of Deposit)</p>
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**INFORMATION DISCLOSURE STATEMENT**  
**UNDER 37 CFR §1.56**

Mail Stop Amendment-IDS  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

Submitted herewith on Form PTO/SB/08 is a listing of documents known to Applicants in order to comply with Applicants' duty of disclosure pursuant to 37 CFR §1.56.

A copy of each non-U.S. patent document and each non-patent document is being submitted to comply with the provisions of 37 CFR §1.97 and §1.98.

The submission of any document herewith, which is not a statutory bar, is not intended as an admission that such document constitutes prior art against the claims of the present application or that such document is considered material to patentability as defined in 37 CFR §1.56(b). Applicants do not waive any rights to take any action which would be appropriate to antedate or otherwise remove as a competent reference any document which is determined to be a *prima facie* art reference against the claims of the present application.

**TIMING OF THE DISCLOSURE**

The listed documents are being submitted in compliance with 37 CFR §1.97(c), before the mailing date of either a final action under 37 CFR §1.113, a notice of allowance under 37 CFR §1.311, or an action that otherwise closes prosecution in the application.

**RELEVANCE OF EACH DOCUMENT**

Applicants respectfully request that each listed document be considered by the Examiner and be made of record in the present application and that an initialed copy of Form PTO/SB/08 be returned in accordance with MPEP §609.

An English translation of the foreign-language document (Reference A6 on PTO/SB/08) is not readily available. The absence of such translation does not relieve the PTO from its duty to consider the submitted foreign language document (37 CFR §1.98 and MPEP §609). However, provided herewith is the Derwent Record (Reference A12 on PTO/SB/08), which contains Derwent's abstract in English of the subject foreign-language document.

**FEE**

A fee in connection with submission of an information disclosure statement under 37 CFR §1.97(c) in the amount of \$180.00 in accordance with 37 CFR §1.17(p) is attached.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 CFR §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50/0872.

Respectfully submitted,

Date March 14, 2006

FOLEY & LARDNER LLP  
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Telephone: (858) 847-6722  
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By Barry S. Wilson

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Attorney for Applicant  
Registration No. 39,431

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Substitute for form 1449B/PTO

**INFORMATION DISCLOSURE  
STATEMENT BY APPLICANT**

Date Submitted: March 13, 2006

Use as many sheets as necessary)

Sheet 1 of 7

**Complete if Known**

Application Number	10/712,584
Filing Date	11/12/2003
First Named Inventor	Francis S. Markland Jr.
Group Art Unit	1631
Examiner Name	Michael L. Borin
Attorney Docket Number	075405-1103

**U.S. PATENT DOCUMENTS**

Examiner Initials*	Cite No. <sup>1</sup>	U.S. Patent Document		Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number	Kind Code <sup>2</sup> (if known)			
	A1	5,731,288		Markland et al.	3/24/98	Abstract, col. 3, col. 4 lines 29-44, Abstract and col. 5 line 59 to col. 6 line 4
	A2	5,814,609		Markland et al.	9/29/98	
	A3	6,710,030		Markland et al.	03/23/04	

**U.S. PATENT APPLICATION DOCUMENTS**

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**FOREIGN PATENT DOCUMENTS**

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		Office <sup>3</sup>	Number <sup>4</sup>	Kind Code <sup>5</sup> (if known)				
	A4		WO 9008772		Biogen Inc.,	8/1990	Abstract, Fig. 9	
	A5		EP 323722		Chiron Corp.,	7/12/1989	Abstract	
	A6		FR 2736266		Mogam Biotechnology Res. Inst.	1/10/1997	Abstract, Fig. 2	
	A7		WO 00/18421		The University of Southern California	4/6/2000	Claims 1-3 and 21-23, examples 6-13	

**NON PATENT LITERATURE DOCUMENTS**

Examiner Initials*	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T <sup>6</sup>
	A8	Albelda et al., "Identification and Characterization of Cell-Substratum Adhesion Receptors on Cultured Human Endothelial Cells," J Clin Invest. 1989 June; 83(6):1992-2002.	

Examiner Signature

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		<b>First Named Inventor</b>	Francis S. Markland Jr.
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		<b>Examiner Name</b>	Michael L. Borin
<b>Sheet</b>	2	<b>of</b>	7
		<b>Attorney Docket Number</b>	075405-1103

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	A9	Bauer et al., "Motility of Fibronectin REceptor-deficient Cells on Fibronectin and Vitronectin: Collaborative Interactions among Integrins," The Journal of Cell Biology, Vol 116, No. 2 1992.	
	A10	Belisario, M.A. et al., "Immobilised echistatin promotes platelet adhesion and protein tyrosine phosphorylation," Biochimica et Biophysica Acta 1497 227-236 (2000).	
	A11	Bhattacharya, S., et al., "Soluble Ligands of the $\alpha_v\beta_3$ Integrin Mediate Enhanced Tyrosine Phosphorylation of Multiple Proteins in Adherent Bovine Pulmonary Artery Endothelial Cells." The Journal of Biological Chemistry 270(28): 16781-16787 (1995).	
	A12	Chung, G.H., et al., "Peptide derived from Korean salmosa viper venom - useful as blood platelet aggregation inhibitor for the management of thrombosis," Derwent Record for FR 2736266 (1997).	
	A13	Clark, E.A., et al., "Structurally Distinct Disintegrins Contortrostatin and Multisquamatin Differentially Regulate Platelet Tyrosine Phosphorylation," The Journal of Biological Chemistry 269 (35):21940-21943 (1994).	
	A14	Cousins G. et al., "Contortrostatin prevents reocclusion after thrombolytic therapy in a canine model of carotid artery thrombosis," Faseb J., vol. 9, no. 4, 1995 abstract.	
	A15	Fujisawa, Y., et al., "Disintegrin, halystatin, from agkistrodon halys, is a potent inhibitor of bone resorption and platelet aggregation," Database Embl, Accession Number D28871 April 8, 1994.	
	A16	Halvorson et al., "The Vitronectin Receptor ( $\alpha_v\beta_3$ ) as an Example for the Role of Integrins in T Lymphocyte Stimulation," Immunologic Research (1996), 15(1), 16-29.	
	A17	Hauzenberger et al., "Triggering of Motile Behavior in T Lymphocytes via Cross-Linking of $\alpha_4\beta_1$ and $\alpha_L\beta_2$ ," Journal of Immunology (1997), 158(1), 76-84.	
	A18	Huang, M., et al., "Adhesive Ligand Binding to Integrin Alpha IIb Beta 3 Stimulates Tyrosine Phosphorylation of Novel Protein Substrates before Phosphorylation of pp 1125 FAK," The Journal of Cell Biology 122(2):473-483 (1993).	
	A19	International Search Report for Application No. PCT/US00/33367.	
	A20	International Search Report for Application No. PCT/US99/22608.	
	A21	Kamiguti AS et al., "Proteolytic cleavage of the beta1 subunit of platelet alpha2beta1 integrin by the metalloproteinase jararhagin compromises collagen-stimulated phosphorylation of pp72," J Biol Chem. 1997 Dec 19;272(51):32599-605.	

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<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>  Date Submitted: March 13, 2006  <i>(use as many sheets as necessary)</i>				Application Number	10/712,584
				Filing Date	11/12/2003
				First Named Inventor	Francis S. Markland Jr.
				Group Art Unit	1631
				Examiner Name	Michael L. Borin
Sheet	3	of	7	Attorney Docket Number	075405-1103

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	A22	Kang, I-C., et al., "A novel disintegrin salmosin inhibits tumor angiogenesis," Cancer Research 59:3754-60 (1999).		
	A23	Kornberg, L., et al., "Cell Adhesion or Integrin Clustering Increases Phosphorylation of a Focal Adhesion-associated Tyrosine Kinase" The Journal of Biological Chemistry 267(33): 23439-23442 (1992).		
	A24	Kornberg, L., et al., "Signal transduction by integrins: Increased protein tyrosine phosphorylation caused by clustering of Beta1 integrins," Proc. Natl. Acad. Sci. USA 88:8392-8396 (1991).		
	A25	C. Chandra Kumar, et al., "Biochemical Characterization of the Binding of Echistatin to Integrin $\alpha_v\beta_3$ Receptor," The Journal of Pharmacology and Experimental Therapeutics Vol. 283, No. 2: pp. 843-853 (1997).		
	A26	Lipfert, L., et al., "Integrin-Dependent Phosphorylation and activation of the Protein Tyrosine Kinase pp125 <sup>FAK</sup> in Platelets." The Journal of Cell Biology 119(4):905-912 (1992).		
	A27	Marcinkiewicz, C. et al., "EC3, a Novel Heterodimeric Disintegrin from Echis Carinatus Venom, Inhibits $\alpha_4$ and $\alpha_5$ integrins in an RGD-independent Manner," The Journal of Biological Chemistry 274 (18): 12468-12473 (1999).		
	A28	Markland, FS et al., "A Novel Snake Venom Disintegrin That Inhibits Human Ovarian Cancer Dissemination and Angiogenesis in an Orthotopic Nude Mouse Model," Haemostasis. 2001 May-Dec;31 (3-6):183-91.		
	A29	Markland, F.S. et al., "Snake Venom Disintegrin: An Effective Inhibitor of Breast Cancer Growth and Dissemination." Chapter 18 in "Natural and Selected Synthetic Toxins, Biological Implications," Tu, A.T. et al. editors, ACS SYMPOSIUM SERIES 745:262-282 (2000).		
	A30	Mercer B. et al., "Contortrostatin, a homodimeric snake venom disintegrin, is a potent inhibitor of osteoclast attachment," J. Bone Min. Res., vol. 13, no. 3, March 1998. see abstract and page 410 left col.		
	A31	Miyamoto, S., et al., "Integrin Function: Molecular Hierarchies of Cytoskeletal and Signaling Molecules," The Journal of Cell Biology 131(3): 791-805 (1995).		

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	A32	Ritter, Matthew R. et al., "Contortrostatin Activates ERK2 and Tyrosine Phosphorylation Events via Distinct Pathways," Biochemical and Biophysical Research Communications 274, 142-148 (2000).	
	A33	Ritter MR et al., "Contortrostatin, a snake venom disintegrin, induces $\alpha_v\beta_3$ mediated tyrosine phosphorylation of CAS and FAK in tumor cells," J Cell Biochem. 2000 Jul 19;79(1):28-37.	
	A34	Ritter, MR et al., "Contortrostatin, a Homodimeric Disintegrin, Actively Disrupts Focal Adhesion and Cytoskeletal Structure and Inhibits Cell Motility Through a Novel Mechanism," Cell Commun. Adhes. 2001;8(2):71-86.	
	A35	Ritter MR et al., "Differential regulation of tyrosine phosphorylation in tumor cells by contortrostatin, a homodimeric disintegrin, and monomeric disintegrins echistatin and flavoridin," Toxicon. 2001 Feb-Mar;39(2-3):283-9.	
	A36	Ritter, M.R. et al., "The Homodimeric Disintegrin Contortrostatin Activates Phosphorylation of FAK and CAS," Molecular Biology of the Cell, Supplement to Molecular Biology of the Cell 10:150a-867 (1999).	
	A37	Sanderson, C. et al., "Vaccinia Virus Induces Ca <sup>2+</sup> -Independent Cell-Matrix Adhesion during the Motile Phase of Infection," Journal of Virology, Vol. 72, No. 12 pp 9924-9933, December 1998	
	A38	Schmitmeier S. et al., "Anti-invasive Effect of Contortrostatin, a Snake Venom Disintegrin, and TNF- $\alpha$ on Malignant Glioma Cells," Anticancer Res. 2000 Nove-Dec;20(6B):4227-33.	

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	A39	Sheu, J.-R. et al., "Inhibition of angiogenesis in vitro and in vivo: comparison of the relative activities of triflavin, an Arg-Gly-Asp-containing peptide and...antibody," Biochimica et Biophysica Acta 1336 445-454 (1997).		
	A40	Sheu, J.R. et al., "Triflavin, an Arg-Gly-Asp-Containing Peptide, Inhibits the Adhesion of Tumor Cells to Matrix Proteins via Binding to Multiple Integrin Receptors Expressed on Human Hepatoma Cells (44038)," TRIFLAVIN AND HUMAN HEPATOMA CELL ADHESION 71-79 (1996).		
	A41	Staiano, N. et al., "Echistatin induces decrease of pp 125 FAK phosphorylation, disassembly of actin cytoskeleton and focal adhesions, and detachment of fibronectin-adherent melanoma cells," European Journal of Cell Biology 73:298-305 (1997).		
	A42	Supplementary Partial European Search Report for US9922608.		
	A43	Supplementary Partial European Search Report for US0033367.		
	A44	Trikha, et al. "A novel platelet aggregation inhibitor from southern copperhead snake venom," Fibrinolysis, International Journal of Fibrinolysis and Thrombolysis, 266 vol. 4, suppl. 1 June 1990.		
	A45	Trikha, et al. "Characterization of a novel platelet aggregation inhibitor (contortrostatin) from the southern copperhead snake venom," The Journal of the American Society of Hematology, Blood vol. 76, no. 10 (Suppl 1), 479a, November 15, 1990.		

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	A46	Trikha M et al., "Contortrostatin, a snake venom disintegrin, inhibits beta 1 integrin-mediated Human metastatic melanoma cell adhesion and blocks experimental metastasis," Cancer Res. 1994 Sep 15;54(18):4993-8.		
	A47	Yeh Chia Hsin, et al., "Accutin, a New Disintegrin, Inhibits Angiogenesis In Vitro and In Vivo by Acting as Integrin $\alpha_v\beta_3$ Antagonist and Inducing Apoptosis" The American Society of Hematology, Blood, vol. 92, No. 9, pp 3268-3276 November 1, 1998.		
	A48	Yeh Chia Hsin, "A new short chain RGD-containing disintegrin, accutin, inhibits the common pathway of human platelet aggregation," Biochimica et Biophysica Acta 1425: pp. 493-504 (1998).		
	A49	Zhou, Q. et al., "Contortrostatin, a dimeric disintegrin from Agkistrodon contortrix contortrix, inhibits angiogenesis," Angiogenesis 3:259-269 (1999).		
	A50	Zhou, Q. et al., "Contortrostatin, a dimeric disintegrin from Agkistrodon contortrix contortrix, inhibits breast cancer progression," Breast Cancer Research and Treatment 61:249-260 (2000).		
	A51	Zhou, Q. et al., "Contortrostatin, a Homodimeric Disintegrin, Binds to Integrin $\alpha_v\beta_5$ ," Biochemical and Biophysical research Communications," 267:350-355 (2000).		
	A52	Zhou Q. et al., "Contortrostatin (CN), A snake venom disintegrin, is an inhibitor of kaposi's sarcoma progression," Proceedings of the Annual Meeting of the American Association for Cancer Research, New York, NY. US vol. 39, 28 April 1998 page 299, abstract.		

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Substitute for form 1449B/PTO <b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b> Date Submitted: March 13, 2006 <i>(use as many sheets as necessary)</i>				<b>Complete if Known</b>	
				Application Number	10/712,584
				Filing Date	11/12/2003
				First Named Inventor	Francis S. Markland Jr.
				Group Art Unit	1631
				Examiner Name	Michael L. Borin
				Attorney Docket Number	075405-1103
Sheet	7	of	7		

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T <sup>6</sup>
	A53	Zhou Q. et al., "Contortrostatin, a snake venom protein, which is an inhibitor of breast cancer progression," Molecular Biology of the Cell, Bethesda MD. US vol. 7, no. Suppl, 7 December 1996. page 425A, abstract.	
	A54	Zhou, Q. et al., " Molecular Cloning and Functional Expression of Contortrostatin, a Homodimeric Disintegrin from Southern Copperhead Snake Venom," Archives of Biochemistry and Biophysics 375(2):278-288 (2000).	

Examiner Signature		Date Considered	
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